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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/882,621	06/15/2001	Erwin Houtzager	4957US	8472

24247 7590 09/23/2004

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EXAMINER	
LEFFERS JR, GERALD G	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 09/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/882,621	HOUTZAGER ET AL.	
	Examiner	Art Unit	
	Gerald G Leffers Jr., PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-52* is/are pending in the application.

4a) Of the above claim(s) *26-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25 and 46-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/14/2004 has been entered.

In the response filed 6/14/2004, several claims were amended (claims 12-13 & 15) and several new claims were added (claims 46-52). Any rejection of record in the instant application not addressed herein is withdrawn. This action is not final.

Election/Restrictions

Applicants elected Group II (claims 12-15) without traverse in the response filed on 12/30/2002. However, upon review of the pending claims and the prosecution history it has been determined that there is sufficient overlap between the phage of Groups I & II that there is no burdensome search requirement in examining these two sets of claims together. Therefore, the inventions of Groups I and II have been REJOINED. The claims under consideration in the instant application are thus claims 1-25 & 46-52. The restriction requirement between claims 1-25, 46-52 and the remainder of the pending claims (i.e. claims 26-45) is still deemed proper and remains in effect. Claims 26-45 remain withdrawn from consideration as being directed to nonelected inventions for reasons of record.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-25 and 46-52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new rejection.**

Each of the rejected claims is directed to a chimeric phage, collections of phage comprising at least one chimeric phage and methods of making a chimeric phage. The chimeric phage of the invention comprises: (i) a fusion protein wherein a proteinaceous molecule is fused to a "functional form" of a phage coat protein, and (ii) a "mutant form" of the same phage coat protein. The "mutant form" is characterized by an inability or reduced ability to mediate infection of a bacterial host in the absence of either the wildtype coat protein or a "functional form" of the coat protein (e.g. a phage comprising no wildtype phage coat protein from which said mutant form is derived and having a coat comprising said mutant form and no copies of said functional form is less infection than a phage comprising no wildtype copies of the coat protein and having a coat comprising said mutant form and at least one copy of the functional form). The claims are enormously broad genus claims in that they encompass literally *any* type of phage (e.g. filamentous phage, phage having an icosahedral head, phage with or without tail structures, phage having ssDNA, dsDNA or RNA genomes, etc.). Further, the claims are directed to

chimeric phage having very specific functional limitations with regard to the specific coat protein that is mutagenized to be inactive in its "mutant form" and to restore infectivity when presented as a "functional form" as part of a fusion polypeptide. Thus, the claims encompass an enormously broad genus of phage and phage coat proteins having very specific functional properties.

The entire disclosure of the specification is directed to the description of particular filamentous phage strains (e.g. M13 or R408) where the g3 protein, which mediates infection of bacterial host cells, is mutated to yield both a "mutant form" (e.g. g3D3 proteins lacking the D1 & D2 domains of the g3 protein) and "functional forms" (e.g. presumably full-length g3 proteins comprising protein fusions at the amino-terminal end of the g3 protein; e.g. see Figure 1). The presence of the g3D3 domain in addition to the g3/fusion "functional form" allows for the stabilization of phage particles that comprise less than 5 copies of the "functional form" and decreases the "background" of particles that do not comprise a functional form because such particles are non-infectious in this system. No other teachings are provided regarding the specific coat proteins that might be used analogously for other types of bacteriophage (e.g. T4, T7, P2, λ, etc.). For example, there is no description of what would be a "functional form" of any of the coat proteins for any other bacteriophage such that the fusion protein comprising the coat protein restores infectious activity to a phage particle comprising a mutant form of the same protein. Thus, the instant specification does not provide any structural/functional basis for the skilled artisan to envision other, non-filamentous embodiments of the claimed chimeric phage.

While there do appear to be filamentous phage systems that appear to meet the recited limitation for the "mutant form" and "functional form" of the coat protein (i.e. see the rejection

under 35 U.S.C. 102(b) over U.S. Patent No. 6,027,930 below), the prior art does not appear to teach other types of chimeric phage (e.g. icosahedral phage such as λ) that would necessarily meet the very specific functional limitations of the claims. In fact, the prior art teaches that assembly of phage particles is an exceedingly complex process. Moody provides a review of phage assembly that describes how different types of phage have tackled the problem of encapsulating the phage genetic material in a protective structure that itself relies on a minimum of genetic information to encode the head structure (Michael F. Moody. Journal of Molecular Biology 1999, Vol. 293, pages 401-433; see the entire document). Generally speaking this involves using a minimum number of different protein subunits (i.e. requiring less genetic information) to form a complex 3-dimensional structure that can accommodate the genetic material (e.g. an icosahedron in the case of large dsDNA bacteriophage). To do this the major head protein subunits must be able to interact with one another in *equivalent* and *quasi-equivalent* ways that involve several protein-protein interactions for each subunit monomer. For example, the different head structures for different types of phage heads shown in Figure 3 of the Moody reference each show how a single protein monomer (represented by the smaller triangles) can interact with itself to form axes of 5-fold or 6-fold symmetry within the same structure. Thus, at each vertex in the structures shown in Figure 3, each monomer of the major head protein can have a 5-fold or 6-fold interaction with adjacent proteins.

Moody teaches that as the required size of the phage head increases (i.e. to encapsulate a larger viral genome) additional proteins are required to help deal with an increased requirement for quasi-equivalent interactions amongst the subunits in assembly of the head structure. For example, these proteins would include endoscaffolding or exoscaffolding proteins and/or other

proteins that can remain as part of the mature phage head (e.g. page 404, last paragraph of column 1 to column 2, second paragraph; page 407, column 1 to page 408, column 2). Moody teaches that assembly of the phage head is a complex process that is liable to errors, resulting in malformed heads such as tubes, spirals or polyhedrons (e.g. page 408, column 2 to page 411, column 1). Moody further teaches that all of the larger dsDNA phage heads undergo some sort of maturation to form a more stable, stronger structure that is more resistant to mechanical or chemical stress and that results in a simultaneous increase in head volume (e.g. page 413, column 2 to page 416, column 1). This process involves modification of at least one of the phage head proteins such as proteolytic cleavage (e.g. T-even phage) or chemical modification (e.g. phage P22, lambda or T7). In the maturation process the protein-protein interactions of the subunits of the phage head are necessarily altered, even resulting in the translocation of subunit domains from the inner to the outer surface of the phage head (e.g. in phage T4) (page 414, columns 1-2). Thus, phage head assembly is a complex process, involving multiple protein-protein interactions that change during the process and involving several different types of proteins. Thus, the prior art provides no basis for the skilled artisan to envision which manipulations of a given coat protein for a given phage will allow the skilled artisan to produce a chimeric phage having the very particular functional properties recited in the rejected claims.

Given the enormous breadth of phage encompassed by the rejected claims, the very specific functional limitations for the recited phage, the complexity of phage morphogenesis and the lack of a structural/functional basis from the instant specification or prior art for the skilled artisan to envision embodiments of the claimed invention other than filamentous phage comprising the g3 protein, the skilled artisan would not have been able to envision a sufficient

number of chimeric phage meeting the functional limitations of the claim to describe the broadly claimed genus of such chimeric phage. Therefore, the skilled artisan would reasonably have concluded applicants were not in possession of the broadly claimed genus of such chimeric phage.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-4, 6-7, 9-11, 16-24 & 46-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **These are new rejections.**

Claim 4 is vague and indefinite in that the metes and bounds of the phrase "a deletion of substantially all" are unclear. It is unclear how much of the D1 and D2 regions can remain and still satisfy the limitation intended by the cited phrase.

Claim 6 is vague and indefinite in that it is unclear the nature and number of steps required in order to obtain a "derivative" of a phage strain. It would be remedial to delete the term "derived from" and substitute therefore the term "obtained from".

Claim 7 is vague and indefinite in that the metes and bounds of the phrase "or a part, analogue or derivative of said peptide or said protein" are unclear. It is unclear what structural/functional requirement is there for a peptide or protein to be a "derivative", "analogue" or simply a "part" of another protein or peptide. For example, is there no functional limitation conveyed by the cited terms? If there is, what degree and type of functional activity is required to satisfy the limitations intended by these terms? Would a single amino acid satisfy the metes

and bounds of being a "part" of a peptide or protein? For that matter, what is the cutoff between being a "peptide" or a "protein". Neither of these terms is explicitly defined in the specification and it is not clear where one begins and the other leaves off.

Claim 9 is vague and indefinite in that it is unclear the nature and number of steps required in order to obtain a "derivative" of a phage coat protein. It would be remedial to delete the term from the claim.

Claim 11 specifies that a particular phage is "stable". This term is not explicitly defined in the specification with regard to a bacteriophage. In what manner and to what degree does the phage have to be "stable" in order to satisfy the claim limitation?

Claims 16 and 19 recite the term "functional equivalents" with regard to phage proteins or a specific arabinose promoter. This term does not appear to be explicitly defined in the specification. In what way and to what degree do the particular proteins or promoters have to be equivalent to the reference protein or promoter in order to satisfy the claim limitation of being "functionally equivalent"?

Claim 20 is vague and indefinite in that there is no clear and positive prior antecedent basis for the phrase "said additional nucleic acid sequence". It appears that it may be remedial to amend the phrase to read "said second nucleic acid".

Claim 24 is vague and indefinite in that the metes and bounds of the phrase "that essentially do not permit homologous recombination" are unclear. How much recombination can occur between the separate nucleic acids and still satisfy the limitation of there being "essentially" no recombination?

Claims 2-4, 46-49 all recite the limitation that the coat protein is "the" g3 protein and/or that "the" g3 protein comprises a mutation in specific domains. There is no clear and positive prior antecedent basis for the term "the g3 protein" in the claims from which the rejected claims depend. For example, phage lambda does not comprise a g3 protein analogous to the one described in the instant specification.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-25 and 46-52 are rejected under 35 U.S.C. 102(b) as being anticipated by Borrebaeck et al (U.S. Patent No. 6,027,930 A; see the entire patent). **This rejection is maintained for reasons of record in the actions mailed 5/20/2003 & 12/16/2003, and is extended to the new claims and claims rejoined with the elected invention in this action. The grounds for rejection are summarized below.**

The '930 patent teaches improved methods for selecting specific bacteriophages wherein the improvement is achieved through a new mutant filamentous helper phage that has retained the gene III promoter and where the gene III encoding sequence is deleted (e.g. Abstract). In particular, Borrebaeck et al teach an example where a chimeric filamentous phage is produced that comprises: (i) a first fusion protein comprising the CT domain of p3 fused to an Fab fragment, and (ii) a second fusion protein comprising the ligand to the Fab fragment fused to a

sufficient portion of the amino-terminal portion of p3 to restore infectivity to the chimeric phage particle. Applicants' own data and the prior art indicate that phage particles comprising only the p3/CT fusion are non-infectious (i.e. they are a "mutant form" of the coat protein as described in the instant specification). The complimenting fusion protein (i.e. the second fusion protein comprising the Fab-specific ligand fused to a functional portion of the p3 protein) acts as the "functional form" of the coat protein in this instance as it restores infectivity to the phage particle. Thus, the '930 patent teaches each of the limitations recited in the rejected claims.

Response to Arguments

Applicant's arguments filed on 6/14/2004 have been fully considered but they are not persuasive. The response essentially argues that while the '930 patent does teach 3 distinct kinds of phage particles, none of them satisfy the limitations of the rejected claims. In particular, the response argues that the third phage particle contains a mutant form of the phage coat protein (i.e. a CT/Fab part coupled to a fusion protein containing hen egg lysozyme and a part of the N-terminal part of p3) which mutant form retains the ability to mediate infection of a natural host by the infectious phage. Thus, the phage does not satisfy the limitation of comprising a "functional form" of the coat protein that renders the chimeric phage particle infection.

This argument is not persuasive because, as indicated above, the two different versions of the coat protein are *different proteins*, one of which satisfies the definition provided by the instant specification for a "mutant form" of the phage coat protein (i.e. the CT/Fab fusion) and the other of which satisfies the definition provided by the instant specification for a "functional form" of the coat protein (i.e. the lysozyme/p3 fusion). There is nothing in the definition or

claims as they are currently written that precludes this interpretation of the teachings of the '930 patent as reading on the rejected claims.

Conclusion

The inventions of claims 1-25 and 46-52 have been rejoined in the instant office action and are under consideration in this application. Claims 26-45 remain withdrawn from consideration as being directed to nonelected inventions. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr., PhD whose telephone number is (571) 272-0772. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gerald G Leffers Jr., PhD
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Art Unit 1636

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PRIMARY EXAMINER

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